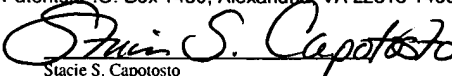


<p align="center">CERTIFICATION OF MAILING UNDER 37 CFR §1.10</p> <p>EXPRESS MAIL MAILING LABEL NUMBER: <i>ER 846 290371 US</i></p> <p>DATE OF DEPOSIT: <i>MARCH 9, 2004</i></p> <p>I hereby certify that this Patent Application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to Mail Stop PATENT APPLICATION, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p align="right">  Stacie S. Capotosto </p>	
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5-O-Mycaminosyltylonide Derivatives

Reference to Related Application

This application is a continuation of Application serial no. 10/125,840 (filed April 19, 2002), which is incorporated herein by reference in its entirety.

Technical Field

The present invention relates to novel macrolides having antibacterial activity that are useful in the treatment and prevention of bacterial infections. More particularly, the present invention relates to a novel class of 16-membered macrolide compounds, compositions containing them, methods for using and processes for making such compounds.

Background of the Invention

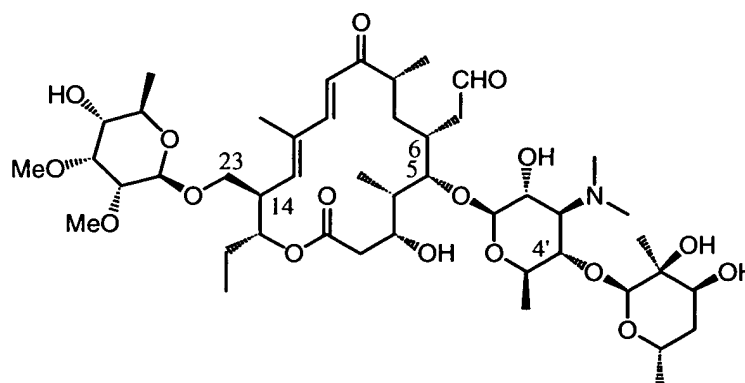
Macrolide antibiotics play a therapeutically important role, particularly with the emergence of new pathogens. Structural differences are related to the size of the lactone ring and to the number and nature (neutral or basic) of the sugars. Macrolides are classified according to the size of the lactone ring (12, 14, 15 or 16 atoms). The macrolide antibiotic families (14-, 15- and 16-membered ring derivatives) exhibit a wide range of characteristics (antibacterial spectrum, side-effects and bioavailability). Among the commonly used macrolides are erythromycin and josamycin.

The 16-membered ring macrolide antibiotics constitute an important clinically useful series of naturally occurring compounds within the macrolide class of antibiotics, as they show some advantages over 14-membered ring compounds (gastrointestinal tolerance and activity against strains expressing resistance of the inducible type). Sixteen membered macrolides usually contain an amino disaccharide-4-O-(L-mycarosyl)-D-mycaminose and/or D-desosamine. One class has only neutral sugars. The sixteen membered

macrolides can be classified into two major series – leucomycin and tylosin series.

The tylosin series is divided into two groups--IIA and IIB--which differ at the C-6-side chain and the nature of the sugars on the chromophore. Tylosin consists of a substituted 16-membered ring lactone (tylonolide), an aminosugar (D-mycaminose)

- 5 attached to C-5, two neutral sugars (D-mycinose attached at C-23 and L-mycarose attached at C-4') and an acetaldehyde at C-6.



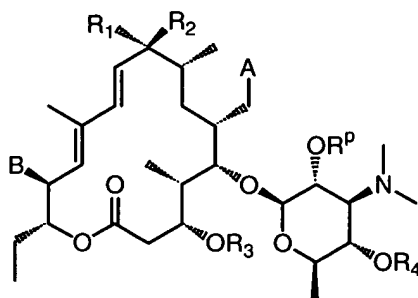
Tylosin

- 10 Considerable research efforts have been carried out on tylosin and its derivatives but not much success has been observed with this subclass. In addition to improving the overall profile of the macrolides in terms of acid stability, tolerance and pharmacokinetics, the search for macrolides active against MLS_B-resistant strains (MLS_B = Macrolides-
- 15 Lincosamides-Type B Streptogramins) has become a major goal.

Summary of the Invention

- The present invention provides a novel class of 5-O-mycaminosyltylonide (OMT) analogs possessing increased antibacterial activity toward Gram positive and Gram negative bacteria as well as macrolide resistant Gram positives. In addition, the present
- 20 invention provides a class of 5-O-mycaminosyltylonide derivatives that are more acid stable and overcome bacterial resistance.

In one embodiment, the present invention provides compounds represented by Formula I, or a pharmaceutically acceptable salt, ester or prodrug thereof:



(I)

In Formula I,

5 A is selected from the group consisting of:

- (1) -CHO or a protected aldehyde;
- (2) -CN;
- (3) -CH=N-NR₅R₆, wherein R₅ and R₆ are each independently selected from the group consisting of:

- 10 (a) hydrogen;
- (b) C₁-C₆-alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic;
- (c) C₂-C₆-alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic;
- 15 (d) C₂-C₆-alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic; and
- (e) R₅ and R₆ taken together with the nitrogen atom to which they are connected to form a 3- to 7-membered ring which may optionally contain one or more heterofunctions selected from the group consisting of: -O-, -NH-, -N(C₁-C₆-alkyl)-, -N(aryl)-, -N(heteroaryl)-, -S-, -S(O)- and -S(O)₂-;

20 (4) -CH=N-OR₅, wherein R₅ is as previously defined;

25 (5) -CH₂X, wherein X is selected from the group consisting of:

- (a) hydroxy or protected hydroxy;
- (b) halogen;
- (c) -NR₅R₆, where R₅ and R₆ are as previously defined;

- (d) $-NR_5C(O)-R_7$, where R_5 is as previously defined and R_7 is selected from the group consisting of:
- i. hydrogen;
 - ii. C_1-C_6 -alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic;
 - iii. C_2-C_6 -alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic;
 - iv. C_2-C_6 -alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic;
 - v. aryl;
 - vi. substituted aryl;
 - vii. heterocyclic; and
 - viii. substituted heterocyclic;
- (e) $-NR_5C(O)-NR_6R_7$, where R_5 , R_6 , and R_7 are as previously defined;
- (f) $-NR_5-NR_6R_7$, where R_5 , R_6 and R_7 are as previously defined;
- (g) $-NR_5-NR_6C(O)-R_7$, where R_5 , R_6 and R_7 are as previously defined;
- (h) $-S(O)_n-R_8$, where R_8 is selected from the group consisting of: aryl, substituted aryl, heterocyclic and substituted heterocyclic, where $n = 0, 1$ or 2 ;
- (i) $-S(O)_n-(C_1-C_6\text{-alkyl})$, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where n is as previously defined;
- (j) $-S(O)_n-(C_2-C_6\text{-alkenyl})$, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where n is as previously defined;
- (k) $-S(O)_n-(C_2-C_6\text{-alkynyl})$, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where n is as previously defined;
- and
- (l) $-O-M-Y$, where M is:

- i. absent,
- ii. $-\text{C}(\text{O})-$,
- iii. $-\text{C}(\text{O})\text{N}(\text{R}_5)-$, where R_5 is as previously defined,
- iv. $-\text{C}_1-\text{C}_6\text{-alkyl-N}(\text{R}_5)-$, where R_5 is as previously defined,
- v. $-\text{C}_2-\text{C}_6\text{-alkenyl-N}(\text{R}_5)-$, where R_5 is as previously defined, or
- vi. $-\text{C}_2-\text{C}_6\text{-alkynyl-N}(\text{R}_5)-$, where R_5 is as previously defined,

and Y is:

- i. hydrogen,
- ii. $\text{C}_1-\text{C}_6\text{-alkyl}$, optionally substituted with one or more substituents selected from the group consisting of: halogen, $-\text{OR}_5$, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where R_5 is as previously defined,
- iii. $\text{C}_2-\text{C}_6\text{-alkenyl}$, optionally substituted with one or more substituents selected from the group consisting of: halogen, $-\text{OR}_5$, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where R_5 is as previously defined,
- iv. $\text{C}_2-\text{C}_6\text{-alkynyl}$, optionally substituted with one or more substituents selected from the group consisting of: halogen, $-\text{OR}_5$, aryl, substituted aryl, heterocyclic and substituted heterocyclic, where R_5 is as previously defined,
- v. aryl,
- vi. substituted aryl,
- vii. heterocyclic, or
- viii. substituted heterocyclic; and

(6) heterocyclic or substituted heterocyclic;

B is selected from the group consisting of:

- (1) $-\text{CHO}$ or a protected aldehyde;
- (2) $-\text{CN}$;
- (3) $-\text{CH}=\text{N}-\text{NR}_5\text{R}_6$, wherein R_5 and R_6 are as previously defined;
- (4) $-\text{CH}=\text{N}-\text{OR}_5$, wherein R_5 is as previously defined;
- (5) $-\text{CH}_2\text{Z}$, wherein Z is selected from the group consisting of:
 - (a) halogen;
 - (b) $-\text{NR}_5\text{C}(\text{O})-\text{R}_7$, where R_5 and R_7 are as previously defined;
 - (c) $-\text{NR}_5\text{C}(\text{O})-\text{NR}_6\text{R}_7$, where R_5 , R_6 , and R_7 are as previously defined;

- (d) $-NR_5-NR_6R_7$, where R_5 , R_6 and R_7 are as previously defined;
- (e) $-NR_5-NR_6C(O)-R_7$, where R_5 , R_6 and R_7 are as previously defined;
- (f) $-S(O)_n-R_8$, where R_8 and n are as previously defined;
- (g) $-S(O)_n-(C_1-C_6\text{-alkyl})$, optionally substituted with one or more substituents
 5 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic and substituted heterocyclic, where n is as previously defined;
- (h) $-S(O)_n-(C_2-C_6\text{-alkenyl})$, optionally substituted with one or more substituents
 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic and substituted heterocyclic, where n is as previously defined;
- (i) $-S(O)_n-(C_2-C_6\text{-alkynyl})$, optionally substituted with one or more substituents
 10 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic and substituted heterocyclic, where n is as previously defined;
 and
- (j) $-NR_9R_{10}$, where R_9 and R_{10} are each independently selected from the group
 15 consisting of:
- i. hydrogen;
 - ii. $C_1-C_6\text{-alkyl}$, optionally substituted with one or more substituents
 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic, $-O-R_5$ and $-NR_5R_6$, where R_5 and R_6 are as previously
 20 defined;
 - iii. $C_2-C_6\text{-alkenyl}$, optionally substituted with one or more substituents
 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic, substituted heterocyclic, $-O-R_5$ and $-NR_5R_6$, where R_5
 and R_6 are as previously defined;
 - iv. $C_2-C_6\text{-alkynyl}$, optionally substituted with one or more substituents
 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic, substituted heterocyclic, $-O-R_5$ and $-NR_5R_6$, where R_5
 and R_6 are as previously defined; and
 - v. $-W-R_{11}$, where W is selected from the group consisting of:
1. $-C(O)-$;
 2. $-C(O)O-$;
 3. $-C(S)-$;
 4. $-C(S)-S-$;
 5. $-C(S)-O-$;
- 30

6. $-\text{C}(\text{S})-\text{N}(\text{R}_5)-$, where R_5 is as previously defined;
 7. $-\text{C}(\text{O})\text{N}(\text{R}_5)-$, where R_5 is as previously defined;
 8. $-\text{C}(=\text{NR}_5)-\text{O}-$, where R_5 is as previously defined; and
 9. $-\text{C}(=\text{NR}_5)-\text{N}(\text{R}_6)-$, where R_5 and R_6 are as previously defined,
 5 and where R_{11} is selected from the group consisting of:
 - a. hydrogen;
 - b. C_1 - C_6 -alkyl, optionally substituted with one or more
 substituents selected from the group consisting of: halogen,
 10 aryl, substituted aryl, heterocyclic and substituted
 heterocyclic;
 - c. C_2 - C_6 -alkenyl, optionally substituted with one or more
 substituents selected from the group consisting of: halogen,
 aryl, substituted aryl, heterocyclic and substituted
 heterocyclic; and
 - 15 d. C_2 - C_6 -alkynyl, optionally substituted with one or more
 substituents selected from the group consisting of: halogen,
 aryl, substituted aryl, heterocyclic and substituted
 heterocyclic;
 - vi. R_9 and R_{10} , taken together with the nitrogen atom to which they are
 20 attached, represent the carbon or hetero atoms necessary to form a
 heterocyclic or substituted heterocyclic moiety; and
 - vii. R_9 and R_{10} , taken together with the nitrogen atom to which they are
 attached, form a 4 to 8 membered ring which contains one or more W
 moieties, and optionally may contain one or more heteromoieties
 25 selected from the group consisting of: $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})_2-$ and $-\text{NR}_5-$,
 where W and R_5 are as previously defined;
- R_1 and R_2 are each independently selected from the group consisting of:
- (1) hydrogen;
 - (2) hydroxy;
 - 30 (3) protected hydroxy;
 - (4) $-\text{OC}(\text{O})-(\text{C}_1-\text{C}_{12}\text{-alkyl})$, optionally substituted with one or more substituents
 selected from the group consisting of: halogen, aryl, substituted aryl,
 heterocyclic, substituted heterocyclic, $-\text{OR}_5$ and $-\text{NR}_5\text{R}_6$ where R_5 and R_6 are
 as previously defined;

- (5) -OR₅, where R₅ is as previously defined;
- (6) halogen;
- (7) -NR₅R₆, where R₅ and R₆ are as previously defined; and
- (8) R₁ and R₂ taken together are = O;

5 R₃ is selected from the group consisting of:

- (1) hydrogen;
 - (2) a hydroxy protecting group;
 - (3) -C(O)-(C₁-C₁₂-alkyl), optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic, substituted heterocyclic, -OR₅ and -NR₅R₆, where R₅ and R₆ are as previously defined;
 - (4) C₁-C₆-alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic, substituted heterocyclic, -OR₅ and -NR₅R₆, where R₅ and R₆ are as previously defined;
 - (5) C₂-C₆-alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic, substituted heterocyclic, -OR₅ and -NR₅R₆, where R₅ and R₆ are as previously defined; and
 - (6) C₂-C₆-alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heterocyclic, substituted heterocyclic, -OR₅ and -NR₅R₆, where R₅ and R₆ are as previously defined;
- R₄ is -M-Y, where M and Y are as previously defined; and
- R^P is hydrogen or a hydroxy protecting group.

25

In another embodiment, the present invention provides processes for preparing novel compounds represented by Formula I wherein the groups A, B, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, M, Y, W and R^P are as previously defined.

30 Detailed Description of the Invention

The present invention relates to compounds represented by Formula I as described above.

Representative compounds of the invention include the following:

- Compound of Formula I: A = -CHO, B = -CH₂-N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- Compound of Formula I: A = -CHO, B = -CH₂-NH-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- 5 Compound of Formula I: A = -CHO, B = -CH₂-N(CH₃)-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- Compound of Formula I: A = -CHO, B = -CH₂-NH-CH₂CH₂-(2-pyridyl) R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- 10 Compound of Formula I: A = -CHO, B = -CH₂-4-morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- Compound of Formula I: A = -CHO, B = -CH₂-1-imidazolyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H;
- Compound of Formula I: A = -CHO, B = -CH₂-N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-quinolyl) and R^P = H;
- 15 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- 20 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(5-pyrimidyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(5-pyrimidyl) and R^P = H;
- 25 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(5-pyrimidyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(phenyl) and R^P = H;
- 30 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(4-fluorophenyl) and R^P = H;

- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(4-fluorophenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(4-fluorophenyl) and R^P = H;
- 5 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(3-quinolyl) and R^P = H;
- 10 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(2-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(2-pyridyl) and R^P = H;
- 15 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(2-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-pyridyl) and R^P = H;
- 20 Compound of Formula I: A = CHO, B = morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-quinolyl) and R^P = H;
- 25 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(5-pyrimidyl) and R^P = H;
- 30 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(5-pyrimidyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(5-pyrimidyl) and R^P = H;

- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(phenyl) and R^P = H;
- 5 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(4-fluorophenyl) and R^P = H;
- 10 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(4-fluorophenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(4-fluorophenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(3-quinolyl) and R^P = H;
- 15 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(2-pyridyl) and R^P = H;
- 20 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(2-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(2-pyridyl) and R^P = H;
- 25 Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CH₂F, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-pyridyl) and R^P = H;
- 30 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-quinolyl) and R^P = H;

- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(5-pyrimidyl) and R^P = H;
- 5 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(5-pyrimidyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(5-pyrimidyl) and R^P = H;
- 10 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(phenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(phenyl) and R^P = H;
- 15 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(4-fluorophenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(4-fluorophenyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(4-fluorophenyl) and R^P = H;
- 20 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CCCH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCHCH₂-(3-quinolyl) and R^P = H;
- 25 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂CH₂-(3-quinolyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(2-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(2-pyridyl) and R^P = H;
- 30 Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(2-pyridyl) and R^P = H;
- Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CC-(3-pyridyl) and R^P = H;

Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CHCH-(3-pyridyl) and R^P = H; and

Compound of Formula I: A = CHO, B = CN, R₁ and R₂ taken together are = O, R₃ = H, R₄ = CH₂CH₂CH₂-(3-pyridyl) and R^P = H.

5

Definitions

The terms "C₁-C₃-alkyl," "C₁-C₆-alkyl" or "C₁-C₁₂-alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and three, one and six or one and twelve carbon atoms, respectively. Examples of C₁-C₃ alkyl radicals include, but are not limited to, methyl, ethyl, propyl and isopropyl, and examples of C₁-C₆-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl and *n*-hexyl, and examples of C₁-C₁₂-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, *n*-octyl, *n*-decyl, and *n*-dodecyl.

The term "C₂-C₆-alkenyl," as used herein, refers to straight- or branched-chain hydrocarbon radicals containing between two and six carbon atoms with one or more double bonds in the chain. Examples of C₂-C₆-alkenyl include, but are not limited to, propenyl, isobutenyl, 1, 3-hexadienyl, *n*-hexenyl, and 3-pentenyl.

The term "C₂-C₆-alkynyl," as used herein, refers to straight- or branched-chain hydrocarbon radicals containing between two and six carbon atoms with one or more triple bonds in the chain optionally containing one or more double bond. Examples of C₂-C₆-alkynyl include, but are not limited to, propynyl, isopentynyl, 1,3-hexadiynyl, *n*-hexynyl, 3-pentynyl, and 1-hexen-3-ynyl.

The term "C₁-C₆-alkoxy," as used herein, refers to a C₁-C₆-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C₁-C₆-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, neopentoxy and *n*-hexoxy.

The term "C₁-C₃-alkyl-amino," as used herein, refers to one or two C₁-C₃-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C₁-C₃-alkyl-amino include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited

to, hydrocarbons such as, for example, hexane and toluene, and the like, halogenated hydrocarbons such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds such as, for example, tetrahydrofuran, N-methyl pyrrolidinone, and the like, and ethers such as, for example, diethyl ether, bis-methoxymethyl ether and the like. Such compounds are well known to those skilled in the art, and it will be apparent to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, for example, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "aryl," as used herein, refers to unsubstituted carbocyclic aromatic groups including, but not limited to, phenyl, 1- or 2-naphthyl and the like.

The terms "C₃-C₅-cycloalkyl- and C₃-C₇-cycloalkyl," as used herein, refer to carbocyclic groups of 3 to 5 or 3 to 7 carbon atoms, respectively, such as for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "C₁-C₃-alkyl-C₃-C₅-cycloalkyl," as used herein refers to a C₃-C₅-cycloalkyl radical, as defined above, attached to a C₁-C₃-alkyl radical by replacement of a hydrogen atom on the latter.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "heteroaryl," as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or more ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 1 double bonds and each 6-membered

ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to a benzene ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, 5 imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "heterocyclic," as used herein, refers to heterocycloalkyl and heteroaryl. The term "substituted heterocyclic," as used herein, refers to substituted heterocycloalkyl and substituted heteroaryl.

10 The term "substituted aryl," as used herein refers to an aryl group, as defined herein, substituted by independent replacement of one or more of the hydrogen atoms therein with, for example, but not limited to, F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, OC(O)-heteroaryl, 15 OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₇- 20 cycloalkyl, CF₃, CH₂CF₃, CH₂Cl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, substituted aryl, heteroaryl, substituted heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkyl-amino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

25 The term "substituted heteroaryl," as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one or more of the hydrogen atoms therein with, for example, but not limited to, F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, 30 OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-

C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, CF₃, CH₂CF₃, CH₂Cl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkyl-amino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

The term "substituted heterocycloalkyl," as used herein, refers to a heterocycloalkyl group, as defined above, substituted by independent replacement of one or more of the hydrogen atoms therein with, for example, but not limited to, F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, CF₃, CH₂CF₃, CH₂Cl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkyl-amino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

The term "substituted cycloalkyl," as used herein, refers to a C₃-C₇ cycloalkyl group, as defined above, substituted by independent replacement of one or more of the hydrogen atoms therein with, for example, but not limited to, F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-

aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, CF₃, CH₂CF₃, CH₂Cl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkyl-amino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

"Hydroxy-protecting group," as used herein, refers to an easily removable group which is known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known. See, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy-protecting groups include, but are not limited to, methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and the like.

The term "protected-hydroxy," refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including, for example, but not limited to, benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups.

"Aldehyde-protecting group," as used herein, refers to an easily removable group which is known to protect an aldehyde group against undesirable reaction during synthetic procedures and to be selectively removable. The use of aldehyde-protecting groups is well known in the art for protecting aldehyde groups against undesirable reactions during a synthetic procedure and many such protecting groups are known. See, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, *op. cit.* Examples of aldehyde-protecting groups include, but are not limited to, acetals, ketals, *O*-substituted cyanohydrins, substituted hydrazones, imines and the like.

The term "protected aldehyde" refers to an aldehyde group protected with an aldehyde protecting group, as defined above, including, for example, but not limited to, dimethyl acetyl, 1,3-dioxolane, 1,3-dioxane and the like.

The term "protogenic organic solvent," as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be apparent to those skilled in the art that individual solvents or

mixtures thereof may be preferred for specific compounds and reaction conditions, for example, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic

5 Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, *op. cit.*.

Numerous asymmetric centers may exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof. Accordingly, whenever a bond is represented by a wavy line, it is intended that a mixture of stereo-orientations or an individual isomer of
10 assigned or unassigned orientation may be present. Further, in those cases where a bond between carbon atoms of the macrolide is a double bond both the cis and trans forms are within the scope of the invention described in this application.

As used herein, the term "pharmaceutically acceptable salt," refers to those salts
15 which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977),
20 incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or
25 with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate,
30 ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate,

sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs," as used herein, refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable risk/reward ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, *Prodrugs as Novel delivery Systems*, Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated by reference herein.

Antibacterial Activity

Susceptibility tests can be used to quantitatively measure the *in vitro* activity of an antimicrobial agent against a given bacterial isolate. Compounds were tested for *in vitro* antibacterial activity by a micro-dilution method. Minimal Inhibitory Concentration (MIC) was determined in 96 well microtiter plates utilizing the appropriate Mueller Hinton Broth medium (CAMHB) for the observed bacterial isolates. Antimicrobial agents were serially diluted (2-fold) in DMSO to produce a concentration range from about 64 µg/ml to about 0.03 µg/ml. The diluted compounds (2µl/well) were then transferred into sterile;

uninoculated CAMHB (0.2 mL) by use of a 96 fixed tip-pipetting station. The inoculum for each bacterial strain was standardized to 5×10^5 CFU/mL by optical comparison to a 0.5 McFarland turbidity standard. The plates were inoculated with 10 μ l/well of adjusted bacterial inoculum. The 96 well plates were covered and incubated at $35 \pm 2^\circ\text{C}$ for 24 hours in ambient air environment. Following incubation, plate wells were visually examined by Optical Density measurement for the presence of growth (turbidity). The lowest concentration of an antimicrobial agent at which no visible growth occurs was defined as the MIC. The compounds of the invention generally demonstrated an MIC in the range from about 64 $\mu\text{g/ml}$ to about 0.03 g/ml .

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In

addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by

entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, powders, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition whereby they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, bacterial infections are treated or prevented in a patient such as a human or other animals by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the

attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from about 0.01 to about 50 mg/kg body weight or more preferably from about 0.1 to about 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of the compounds of the present invention per day in single or multiple doses.

The pharmaceutical compositions of this invention can be administered to fish by blending them in the fish feed to be administered orally or may be dissolved in water in which sick fish are placed to swim around (a method using a so-called "medicated bath").

The dosage for the treatment of fish differs depending upon the purpose of administration (prevention or cure of disease) and type, size and extent of infection of the fish to be treated. Generally, a dosage of 5 – 1000 mg, preferably 20 – 100 mg, per kg of body weight of fish may be administered per day, either at one time or divided into several times. It will be recognized that the above specified dosage is only a general range which may be reduced or increased depending on the age, body weight, condition of disease, etc. of the fish.

Abbreviations

Abbreviations which have been used in the descriptions of the scheme and the examples that follow are: AIBN for azobisisobutyronitrile; BOC for tert-butoxycarbonyl; Bu₃SnH for tributyltin hydride; BSA for bis(trimethylsilyl)acetamide; CDI for carbonyldiimidazole; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC for 1,3-dicyclohexylcarbodiimide; DEAD for diethylazodicarboxylate; DIC for 2-chloro-N,N-

dimethylpropylamine, hydrochloride, DIEA for diisopropylethylamine; DMF for dimethyl formamide; DMSO for dimethyl sulfoxide; DPPA for diphenylphosphoryl azide; EtOAc for ethyl acetate; HMDS for 1,1,1,3,3,3-hexamethyldisilazane; MeOH for methanol; NaN(TMS)₂ for sodium bis(trimethylsilyl)amide; NMO for N-methylmorpholine N-oxide;

5 PCC for pyridinium chlorochromate; PDC for pyridinium dichromate; TEA for triethylamine; THF for tetrahydrofuran; TPP for triphenylphosphine; DMAP for 4- N,N-dimethylamino pyridine; TFA for trifluoroacetic acid; KHMDS for potassium bis(trimethylsilyl)amide; Ac for acetyl; Bz for benzoyl; TBAF for tetrabutyl ammonium fluoride; m-CPBA for meta-chloro perbenzoic acid; TBDMSCl for tert-butyl dimethyl silyl

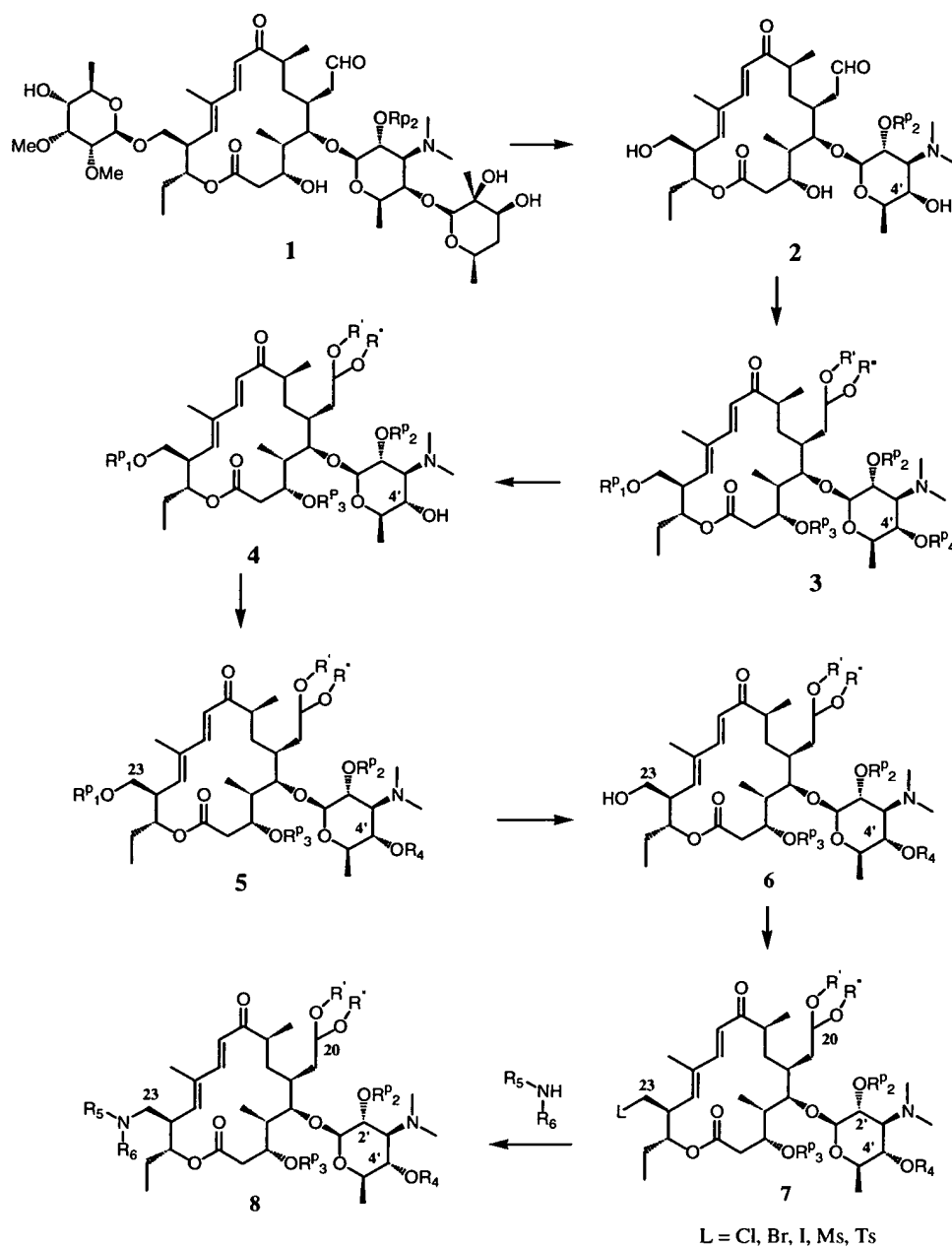
10 chloride; TES for triethylsilyl; TMS for trimethylsilyl and TBDPSCl for tert-butyldiphenyl silyl chloride.

Synthetic Methods

The compounds and processes of the present invention will be better understood in

15 connection with the following synthetic schemes which are illustrative of the methods by which the compounds of the invention may be prepared. The groups A, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R^p are as defined previously unless otherwise noted below. The groups R^p₁, R^p₂, R^p₃ and R^p₄ are hydroxy-protecting groups and the groups R' and R'' are C₁-C₆-alkyl or taken together are -CH₂CH₂- or -CH₂CH₂CH₂-.

Scheme 1



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One synthetic method of the present invention pertains to the preparation of the compounds of Formula I by treating 2'-protected tylosin (**1** of Scheme 1) with a dilute aqueous acid (0.1-5 N), such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, trifluoroacetic acid, acetic acid, or the like or combinations thereof, optionally in an organic solvent such as acetone, acetonitrile, methanol, ethanol or the like, or combinations thereof, at a temperature from about 0°C to about 100°C for about 1 to 24 hours, to provide

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protected **2**, where R^P_2 is an ester. **2** is treated with acetyl chloride, hydrochloric acid, acetic acid, or the like, to provide a solution of pH from about 1 to about 4 in an alcoholic solvent, such as methanol, ethanol, ethylene glycol, or the like, to provide an acetal intermediate. The acetal intermediate is further treated with a silylating agent, such as

5 HMDS, BSA, triethylsilyl chloride, TBDMSCl, TBDPSCI, or the like, optionally with the addition of a catalyst, such as DMAP, imidazole or the like, in an aprotic solvent such as methylene chloride, ethylene chloride, THF, chloroform, DMF, acetonitrile, or the like, at a temperature from about 0°C to about 50°C for about 1 to 48 hours to provide **3**. Selective deprotection at the 4'-position in **3** is achieved by treating **3** with an acid such as formic

10 acid, acetic acid, propanoic acid, phenolic acid, or the like, in an organic solvent such as acetone, acetonitrile, methanol, ethanol, or the like or combinations thereof, at a temperature from about 0°C to about 50°C for about 1 to 24 hours to provide **4**. **4** is reacted with an alkylating agent, such as an alkyl halide, alkyl sulphonate, propargyl halide, allyl halide, arylallyl halide, heteroarylallyl halide, benzyl halide, or the like, in the

15 presence of a base, such as sodium hydride, potassium hydride, potassium tert-butoxide, potassium hydroxide, KHMDS, or the like, in an aprotic solvent such as THF, DMSO, DMF, dioxane, or the like or mixtures thereof, at a temperature from about -20°C to about 60°C to provide **5**. Further selective deprotection of the siloxyl group at the C-23 position in **5** can be effected by treatment with an acid, such as acetic acid, propanoic acid, or the

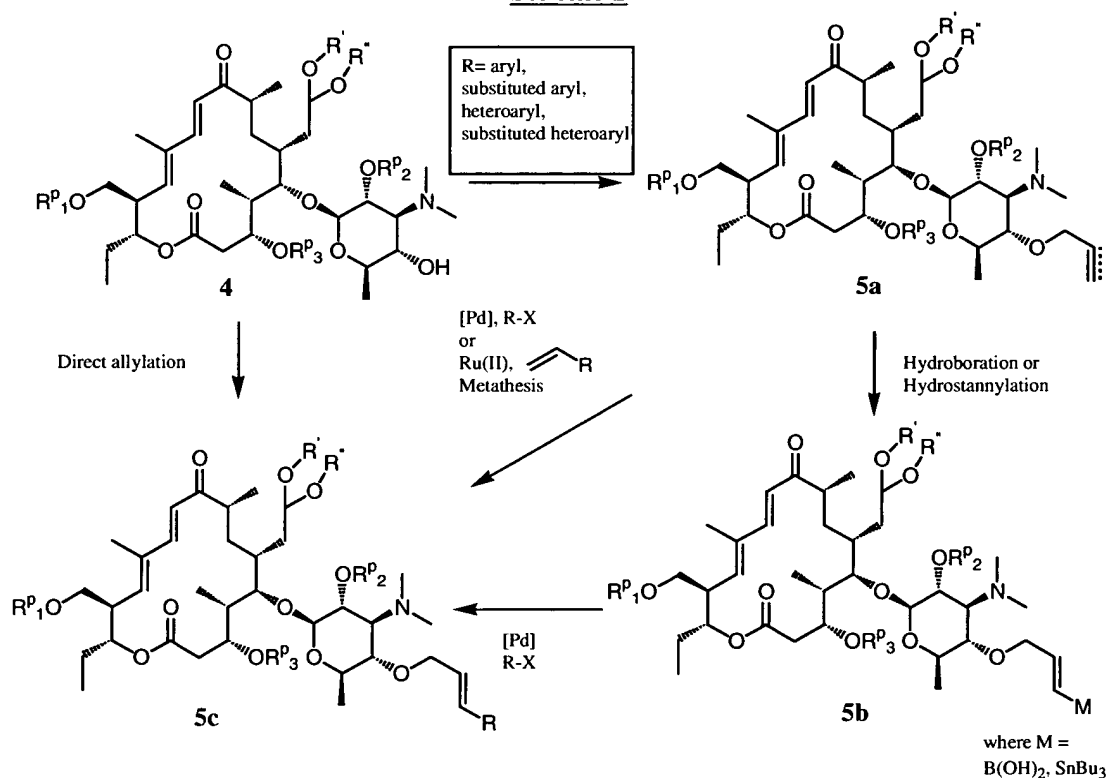
20 like, in an organic solvent, such as acetone, acetonitrile, methanol, ethanol, or the like or combinations thereof, at a temperature from about room temperature to about 100°C for about 1 to 48 hours to provide **6**. **6** can be further derivatized to **7**, where L is a halide, such as chloride, bromide or iodide, by treating with triphenylphosphine and a halogenating agent, such as chlorine, bromine, iodine, carbon tetrachloride, carbon tetrabromide, carbon

25 tetraiodide or the like, in an aprotic organic solvent, such as methylene chloride, ethylene chloride, THF, chloroform, DMF, acetonitrile, or the like, at a temperature from about -78°C to about 50°C for about 30 minutes to 48 hours. **7**, where L is a sulfonate such as mesylate (Ms) or tosylate (Ts), can be prepared by treating **6** with the corresponding sulfonic anhydride, sulfonyl chloride or mixed anhydride in an aprotic organic solvent such

30 as methylene chloride, ethylene chloride, THF, chloroform or the like at a temperature from about -78°C to about 50°C for about 30 minutes to 48 hours in the presence of an amine base, such as pyridine, diethylamine, triethylamine or the like, optionally by adding a catalyst such as DMAP, imidazole or the like. **8** is obtained by treating **7** with the corresponding amine (for example, NHR_5R_6) in a solvent such as water, ethanol, THF,

DMF, DMSO, 1,4-dioxane, or the like, or combinations thereof, at a temperature from about 0°C to about 100°C for about 1 to 24 hours. Deprotection at the C-20 acetal and C-3 siloxyl group in **7** and **8** can be carried out in one step by treating with an aqueous acid, such as sulfuric acid, hydrochloric acid, hydrofluoric acid, acetic acid or the like in an organic solvent, such as acetone, acetonitrile, THF, DMF, DMSO, 1,4-dioxane, or the like, or combinations thereof, at a temperature from about 0°C to about 100°C for about 1 to 24 hours, to provide a 2'-protected intermediate. Further removal of the R^P₂ protecting group at the 2'-position, where R^P₂ is an ester, can be done by stirring in methanol at a temperature from about room temperature to about reflux temperature to provide compounds of Formula I.

Scheme 2



Another synthetic method of the present invention pertaining to the preparation of compounds of Formula I is illustrated in Scheme 2. **5a** of Scheme 2 is obtained by alkylating **4** with allyl bromide or propargyl bromide, as described in Scheme 1. The propargyl group of **5a** is reduced with a variety of borane reagents, such as catecholborane, BH₃, thexylborane, or the like, to give the vinyl boronic acid derivative or stannane reagents, such as tributyltin hydride, to give vinyl stannane derivatives, to provide **5b**. **5c** is obtained by subjecting **5b** to further palladium catalyzed Suzuki or Stille coupling reactions

with R-X, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, and X is a halide or triflate (*see* (a) Suzuki, *Chemical Reviews*, **1995**, *95*, 2457; (b) Suzuki, *Pure & Appl. Chem.* **1991**, *63*, 419; (c) Reviews: Farina, V., Krishnamurthy, V., and Scott, W. J., *The Stille Reaction*, 1st ed.; Wiley, New York, 1998.). In addition, **5a** is treated with

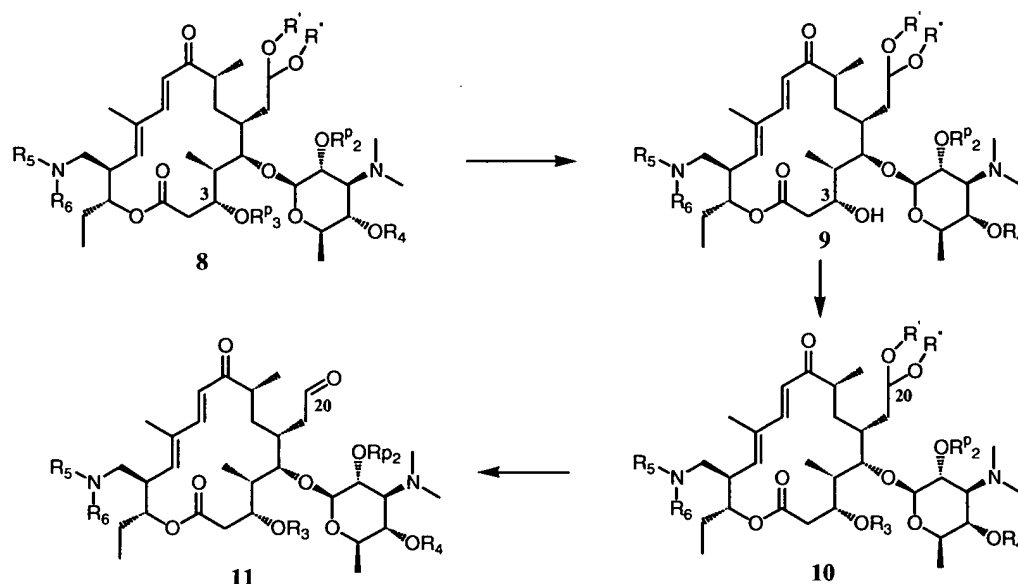
5 R-X, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, and X is a halide or triflate, in the presence of a palladium catalyst [Pd(0) or Pd(II)] to provide **5c** (*see* (a) Heck, *Palladium Reagents in Organic Synthesis*, Academic Press: New York, **1985**, Chapter 1; (b) Sonogashira, *Comprehensive Organic Synthesis*, Volume 3, Chapters 2,4; (c) Sonogashira, *Synthesis* **1977**, 777). Under the Heck coupling conditions,

10 regioisomers and stereoisomers of the double bond are possible. Alternatively, **5a** can undergo a cross metathesis reaction with vinylaromatic derivatives, such as CH₂=CH-R, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, using ruthenium catalysts to provide **5c** (*see* (a) *J. Org. Chem.* **2000**, *65*, 2204-2207; (b) Reviews: *Synlett.* **1999**, *2*, 267; (c) Reviews: Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis*

15 *Polymerization*, 2nd ed.; Academic Press: New York, 1997; (d) *J. Org. Chem.* **1999**, *64*, 4798-4816; (e) *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036-2056; (f) *Tetrahedron* **1998**, *54*, 4413-4450). Alternatively **4** of Scheme 2 is reacted with a tert-butyl allyl carbonate catalyzed by a palladium catalyst [Pd(0) or Pd(II)] to provide **5c** directly (*see* (a) Trost, B. M. *Angew. Chem. Int. Ed. Eng.* **1989**, *28*, 1179. (b) Heck, *Palladium Reagents in Organic*

20 *Synthesis*, Academic Press: New York, **1985**, Chapter 1; and (c) Tsuji *Tetrahedron Lett.* **1992**, *33*, 2987). **5c** is further transformed to compounds of formula I as described in Scheme 1 (such as for the transformation of **5** to **8**).

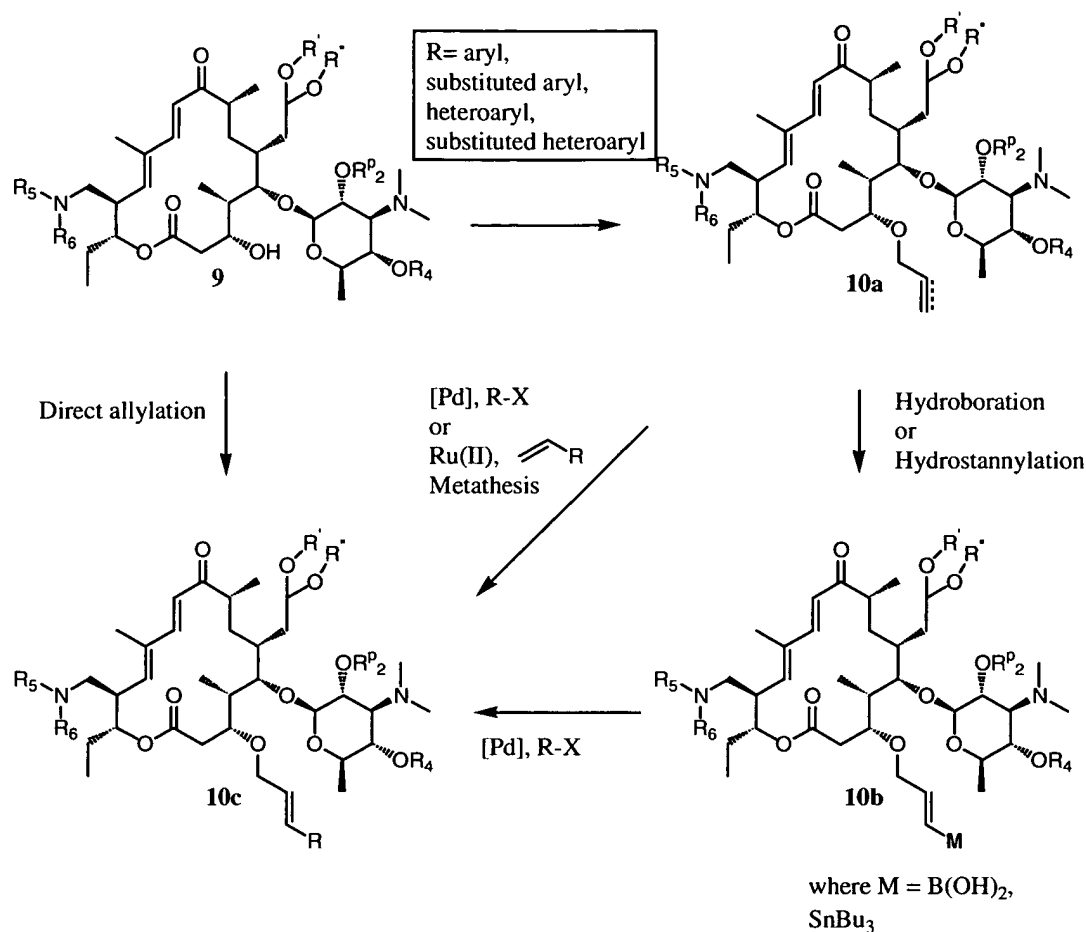
Scheme 3



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Yet another synthetic method of the present invention pertains to the preparation of the compounds of Formula I as illustrated in Scheme 3. **8** of scheme 3 is treated with TBAF or hydrofluoric acid to remove the C-3 silyl protecting group to provide **9**. **9** is reacted with an alkylating agent, such as an alkyl halide, alkyl sulphonate, propargyl halide, allyl halide, arylallyl halide, heteroarylallyl halide, benzyl halide or the like, in the presence of a base, such as sodium hydride, potassium hydride, potassium tert-butoxide, potassium hydroxide, KHMDS, or the like, in an aprotic solvent such as, THF, DMSO, DMF, 1,4-dioxane, or the like, or mixtures thereof, at a temperature from about -20°C to about 60°C , to provide **10**. Deprotection of the C-20 acetal group can be effected by aqueous acidic solution, such as sulfuric acid, hydrochloric acid, hydrofluoric acid, acetic acid or the like, with optionally added organic solvent such as acetone, acetonitrile, THF, 1,4-dioxane or the like, or combinations thereof, at a temperature from about 0°C to about 100°C for 1 – 24 hours to provide a 2'-protected intermediate **11**. Further removal of the R^P₂ protecting group at the 2'-position, where R^P₂ is an ester, can be done by stirring in methanol at a temperature from about room temperature to about reflux temperature, to provide compounds of Formula I.

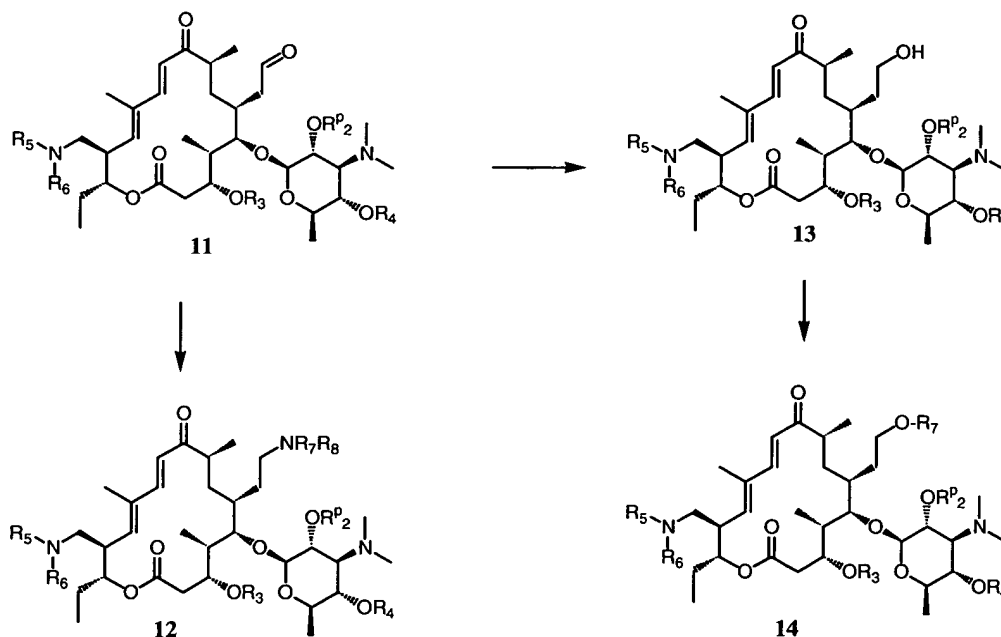
Scheme 4



Another synthetic method of the invention pertains to the preparation of compounds of Formula I as illustrated in scheme 4. **10a** in scheme 4 is obtained by alkylating **9** with allyl bromide or propargyl bromide, as described earlier in scheme 3. The propargyl group of **10a** is reduced with a variety of borane reagents, such as catecholborane, BH_3 , thexylborane, or the like, to give the vinyl boronic acid derivative or stannane reagents, such as tributyltin hydride, to give vinyl stannane derivatives **10b**. **10c** is obtained by subjecting **10b** to further palladium catalyzed Suzuki or Stille coupling reactions with R-X, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, and X is a halide or triflate (*see* (a) Suzuki, *Chemical Reviews*, **1995**, 95, 2457; (b) Suzuki, *Pure & Appl. Chem.* **1991**, 63, 419; and (c) Reviews: Farina, V., Krishnamurthy, V., and Scott, W. J., *The Stille Reaction*, 1st ed.; Wiley, New York, 1998). In addition, **10a** is treated with R-X, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, and X is a halide or triflate, in the presence of a palladium catalyst [Pd(0) or Pd(II)] to provide **10c** (*see* (a) Heck, *Palladium Reagents in Organic Synthesis*, Academic Press: New York, **1985**,

Chapter 1; (b) Sonogashira, *Comprehensive Organic Synthesis*, Volume 3, Chapters 2 and 4; (c) Sonogashira, *Synthesis* **1977**, 777). Under the Heck coupling conditions, regioisomers and stereoisomers of the double bond are possible. Alternatively, **10a** can undergo a cross metathesis reaction with vinylaromatic derivatives, such as $\text{CH}_2=\text{CH-R}$, where R is an aryl, heteroaryl, substituted aryl, or substituted heteroaryl group, using ruthenium catalysts to provide **10c** (see (a) *J. Org. Chem.* **2000**, 65, 2204-2207; (b) Reviews: *Synlett.* **1999**, 2, 267; (c) Reviews: Ivin, K. J., and Mol, J. C., *Olefin Metathesis and Metathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997; (d) *J. Org. Chem.* **1999**, 64, 4798-4816; (e) *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2036-2056; and (f) *Tetrahedron* **1998**, 54, 4413-4450). Alternatively, **9** of scheme 4 is reacted with a tert-butyl allyl carbonate or tert-butyl arylallyl carbonate catalyzed by a palladium catalyst [Pd(0) or Pd(II)] to provide **10a** or **10c** directly (see (a) Trost, B. M. *Angew. Chem. Int. Ed. Eng.* **1989**, 28, 1179; (b) Heck, *Palladium Reagents in Organic Synthesis*, Academic Press: New York, **1985**, Chapter 1; (c) Tsuji *Tetrahedron Lett.* **1992**, 33, 2987).

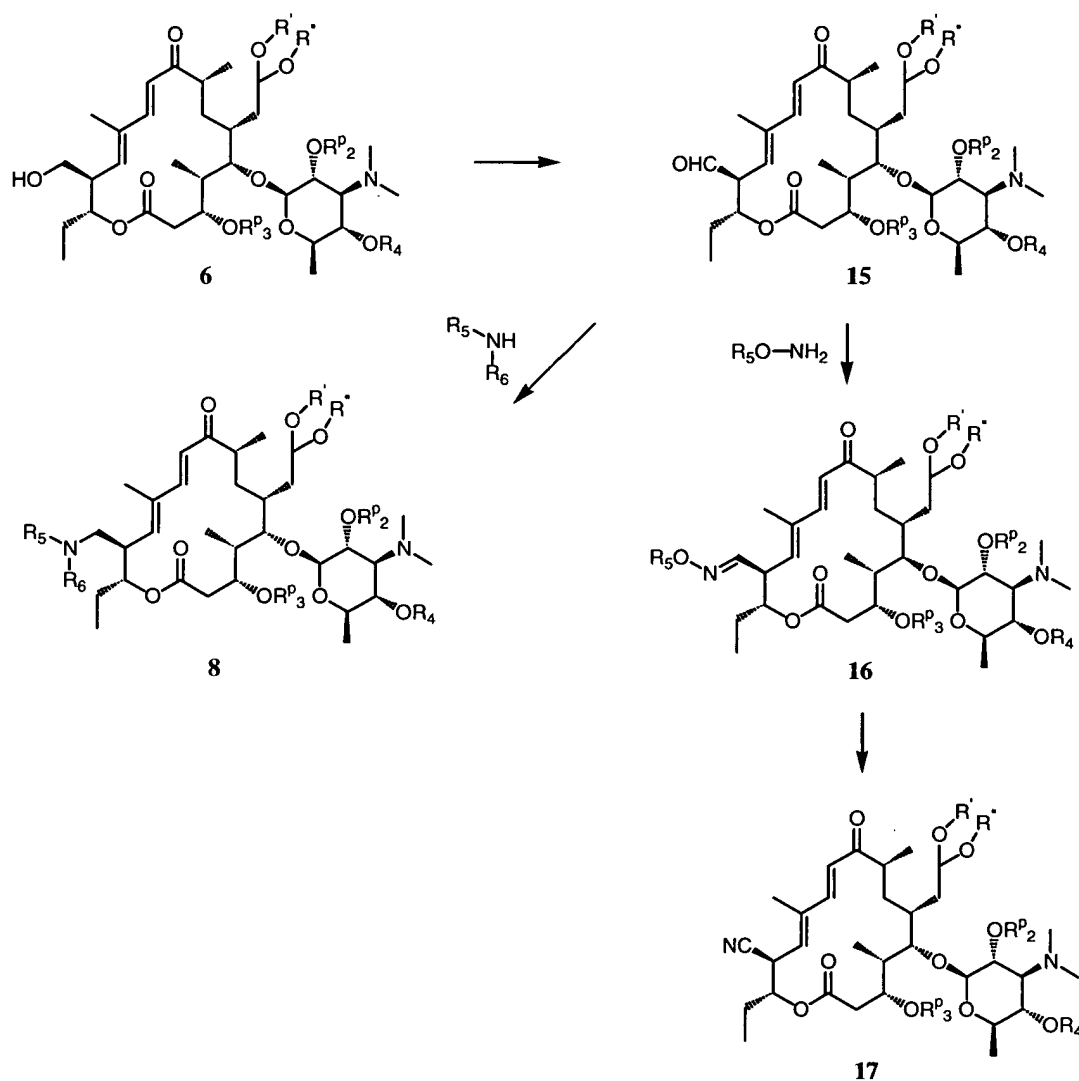
Scheme 5



Scheme 5 illustrates yet another synthetic method of the present invention for the preparation of the compounds of Formula I. **11** in Scheme 5 can be derivatized to an amino derivative *via* reductive amination methods, for example, by treating with an amine compound in the presence of sodium borohydride, sodium cyanoborohydride, or the like, in

an alcoholic solvent, such as methanol, ethanol or isopropanol or acetonitrile or the like, at a pH from about 2 to about 6, to provide **12**. **11** can also be reduced to the corresponding alcohol with various hydride reducing agents, such as sodium borohydrides, lithium borohydrides, or the like, in an organic solvent such as methanol, ethanol, isopropanol, 5 acetonitrile, THF, or the like, to provide **13**. **13** can be converted to an ether compound of the invention by treatment with an alkyl halide, alkyl sulphonate, propargyl halide, allyl halide, arylallyl halide, heteroarylallyl halide, benzyl halide or the like, in the presence of a base, such as sodium hydride, potassium hydride, potassium tert-butoxide, potassium hydroxide, KHMDS, or the like, in an aprotic solvent, such as THF, DMSO, DMF, 10 dioxane, or the like or mixtures thereof, at a temperature from about -20°C to about 60°C to provide **14**. The R^{P}_2 protecting group at the 2'-position in **12**, **13** and **14** can be removed by stirring in methanol at a temperature from about room temperature to about reflux temperature, where OR^{P}_2 is an ester, to provide compounds of Formula I.

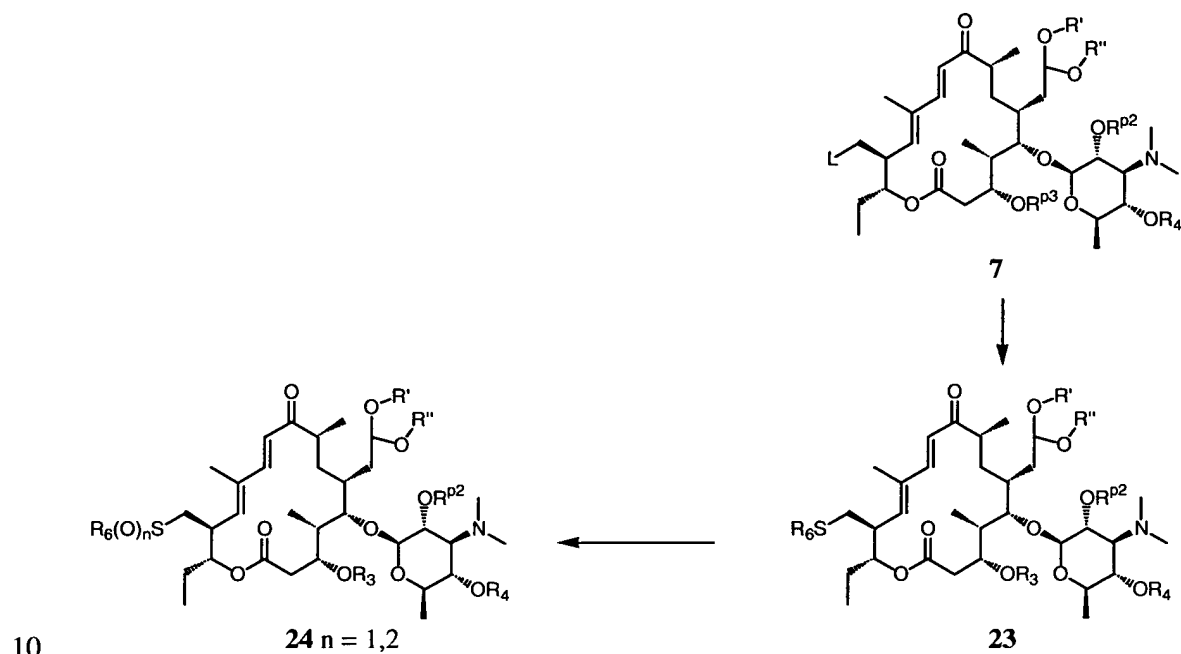
Scheme 6



Another synthetic method of the present invention, Scheme 6, pertains to the preparation of compounds of Formula I. In Scheme 6, 6 is oxidized with an oxidant, such as PCC, PDC, chromium trioxide, or the like, or DMSO and the like, and an electrophilic reagent such as dicyclohexylcarbodiimide, trifluoroacetic anhydride, acetic anhydride, oxalyl chloride, sulfur trioxide, or the like, in an organic solvent such as methylene chloride, chloroform, ethylene chloride, or the like, at a temperature from about - 45°C to about 25°C for about 1 to 48 hours, to provide 15. 15 is treated with an amine compound in the presence of sodium borohydride, sodium cyanoborohydride, or the like, in an alcoholic solvent such as methanol, ethanol or isopropanol or in acetonitrile, or the like, at a pH from about 2 to about 6, to provide 8. Treating 15 with a hydroxylamine of the general formula R₅ONH₂ where R₅ is as previously defined, in an alcoholic solvent such as methanol,

ethanol or isopropanol, or in acetonitrile, optionally adding an acid catalyst such as acetic acid, hydrochloric acid, or the like, optionally with the addition of a base such as imidazole, DMAP, or the like, provides **16**. **16**, when R_5 is hydrogen, can be dehydrated by treating with DCC, DIC, or the like in an organic solvent such as methylene chloride, chloroform, dichloroethane, THF, or the like, and optionally adding cuprous chloride to give **17**. **15**, **16** and **17** can be further deprotected as previously described in Schemes 1-5 to provide compounds of Formula I.

Scheme 7



Another process of the invention for the preparation of the compounds of Formula I comprises derivatization of **7** of Scheme 7 to **23** by treating with a mercaptan such as methyl mercaptan, benzenethiol, benzyl mercaptan, or the like, in an organic solvent such as acetonitrile, THF, methylene chloride, or the like or mixtures thereof, at from about -20°C to about 100°C , optionally containing water (1-90% in volume), in the presence of a base such as lutidine, DBU, DMAP, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, potassium *tert*-butoxide, potassium hydroxide, KHMDS, or the like, optionally added a phase-transfer catalyst such as tetrabutylammonium iodide, benzyltriethylammonium chloride, *n*-cetyltrimethylammonium bromide, tetraphenylphosphonium bromide, 18-crown-6, or the like. **23** can be further oxidized to **24** where $n = 1$ or 2 with an oxidant such as PCC, PDC, chromium trioxide, MnO_2 , RuO_4 ,

oxone, or the like, at about -45°C to about 25°C for about 1 to 48 hours. **23** and **24** can be deprotected as previously described to give compounds of Formula I.

Examples

5 The synthetic methods described above for preparation of compounds of Formula I of the present invention will be better understood in connection with the following examples, which are intended to be illustrative only, and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without
10 limitation, those relating to the chemical structures, substituents, derivatives, syntheses, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1

15 Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H, and R^P = H

Step 1a. Compound Formula I: A = -CH(OCH₃)₂, B = -CH₂OH, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

20 Into a solution of the compound of formula I, where A = CHO, B = -CH₂OH, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃ (6.1 g, 8.9 mmol) in methanol (20 mL), was added dropwise at 0°C a solution of acetic chloride (2 mL) in methanol (10 mL). The reaction mixture was stirred for 40 minutes at 0°C . After addition of a solution of saturated sodium bicarbonate, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under
25 reduced pressure to give the title compound (6.3 g, 97%) as a white solid.
MS (ESI) m/z 728 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.9, 173.6, 169.7, 169.2, 155.3, 147.4, 141.6, 135.7, 118.6, 102.4, 102.0, 81.2, 74.9, 71.5, 70.9, 70.5, 67.1, 62.2, 60.3, 53.5, 49.9, 47.1, 41.1, 39.7, 32.8, 30.9, 25.2, 21.3, 21.1, 20.9, 17.7, 17.1, 14.1, 13.0, 9.6, 8.6.

30 Step 1b. Compound of Formula I: A = -CH(OCH₃)₂, B = -CH₂OMs, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

 Into the solution of the compound from step 1a (5.00 g, 6.87 mmol) in dichloromethane (20 mL), was added methanesulfonic anhydride (1.32 g, 7.56 mmol) and triethylamine (1.04 g, 10.30 mmol) at 0°C . The reaction mixture was stirred for 5 minutes,

then warmed up to room temperature and stirred for 2 hrs. The reaction mixture was again cooled to 0°C. Additional methanesulfonic anhydride (70 mg, 0.40 mmol) was added. The mixture was stirred for 30 minutes, quenched by addition of water (200 mL) and extracted with dichloromethane. The extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give essentially pure title compound (5.50 g, 6.82 mmol).

MS (ESI) m/z 806 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.5, 173.4, 169.7, 169.2, 149.1, 146.5, 138.1, 136.3, 119.5, 102.3, 102.0, 82.9, 81.1, 73.7, 71.4, 70.9, 70.5, 67.7, 67.1, 53.5, 53.4, 49.8, 47.0, 44.9, 44.0, 41.1, 39.6, 37.5, 30.8, 25.1, 21.2, 21.1, 17.6, 17.1, 14.1, 13.0, 9.4, 8.6.

10 Step 1c. 7 of Scheme 1: L = I, R^P₂ = -COCH₃, R^P₃ = H, R₄ = -COCH₃, and R' = R'' = -CH₃;

Into a solution of the compound from step 1b (5.50 g, 6.82 mmol) in acetone (20 mL), was added NaI (8.3 g, 55 mmol) at room temperature. The mixture was stirred under N₂, with the absence of light for 16 hours. The mixture was taken up in CHCl₃, washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the crude title compound (6.0g). The pure title compound can be obtained by further purification on silica (EtOAc:Hexanes/1:1).

MS (ESI) m/z 838 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.7, 173.4, 169.7, 169.2, 146.9, 142.4, 135.5, 119.2, 102.4, 102.1, 81.2, 76.8, 71.5, 70.9, 70.5, 67.2, 60.3, 53.5, 49.9, 45.6, 41.2, 39.7, 32.8, 30.9, 24.7, 21.3, 21.2, 20.9, 17.7, 17.1, 14.1, 13.2, 14.1, 13.2, 9.5, 8.6.

20 Step 1d. 8 of Scheme 1: R₄ = -COCH₃, R₅ = R₆ = -CH₃, R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

Into the solution of the crude compound from step 1c (6.0 g) in acetonitrile (50 mL), was added excess dimethylamine (17.2 mL of 2 M solution in THF, 34.3 mmol) at room temperature. The reaction mixture was heated to 60°C for 1.5 hours, cooled to room temperature, stirred overnight, and concentrated under reduced pressure. The resulting crude residue was taken up in CHCl₃, washed with saturated NaHCO₃ aqueous solution, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the title compound (5.20 g).

30 MS (ESI) m/z 755 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.6, 173.6, 169.7, 169.2, 147.7, 144.6, 134.2, 102.4, 102.1, 81.4, 76.2, 71.5, 70.9, 70.6, 67.2, 61.0, 53.5, 49.9, 45.8, 43.3, 41.2, 39.6, 31.5, 31.0, 25.6, 21.3, 21.2, 17.7, 17.2, 14.0, 12.9, 9.6, 8.7.

Step 1e. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃, and R^P = -COCH₃;

Into a solution of the compound from step 1d (80 mg) in THF (1 mL) was added 1N HCl (1 mL). The mixture was stirred for 2 hours at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with chloroform. The extract was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give pure title compound (65 mg).

MS (ESI) m/z 709 (M+H)⁺.

¹³C-NMR(100 MHz, (CDCl₃):

δ 203.0, 173.7, 169.7, 169.2, 148.2, 144.5, 134.4, 117.7, 101.8, 80.8, 76.3, 71.4, 71.0, 70.5, 67.9, 67.1, 66.6, 61.1, 53.4, 45.8, 45.0, 43.5, 43.3, 41.2, 40.7, 39.3, 31.6, 31.0, 25.7, 25.5, 21.3, 21.2, 17.4, 17.2, 13.0, 9.6, 8.5.

Step 1f. Compound of Formula I A = CHO, B = -N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H, and R^P = H.

A solution of the compound from Step 1e (65 mg) in methanol (1 mL) was stirred at room temperature for twelve hours, and the solvent evaporated under reduced pressure to give the title compound (63 mg).

MS (ESI) m/z 625 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃):

δ 203.1 (2X), 173.8, 148.3, 144.6, 134.4, 117.9, 103.9, 77.2, 76.3, 73.3, 70.9, 70.8, 70.0, 61.1, 53.4, 50.6, 45.8, 44.8, 43.7, 43.3, 41.6, 39.3, 30.2, 29.6, 25.8, 17.7, 17.4, 12.9, 9.6, 8.9

Example 2

Compound of Formula I: A = -CHO, B = -CH₂NH-CH₂CH₂Phenyl, R₁ and R₂ taken

together are = O, R₃ = H, R₄ = H, and R^P = H.

Step 2a. 8 of Scheme 1: R₄ = -COCH₃, R₅ = -CH₂CH₂Phenyl, R₆ = H, R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

Into a solution of the compound from step 1c (150 mg, 0.18 mmol) in DMF (0.5 mL), was added phenethylamine (24 mg, 0.2 mmol) at room temperature. The reaction mixture was heated at 80°C for 7 hours, cooled to room temperature and stirred overnight. The mixture was taken up in EtOAc, washed with a saturated aqueous solution of NaHCO₃, washed with brine and dried (Na₂SO₄), filtered and concentrated under reduced pressure to

provide the crude product (155 mg). The crude residue was further purified by flash chromatography (EtOAc:Hexanes/1:1) to give the title compound (59 mg).

MS (ESI) m/z 831 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.8, 173.7, 169.7, 169.2, 147.1, 142.7, 139.6, 136.4,
 5 128.5, 128.4, 126.3, 118.7, 102.4, 102.1, 81.3, 75.8, 71.5, 70.9, 70.6, 67.2, 53.5, 51.3, 50.3,
 49.9, 45.5, 45.0, 41.2, 39.7, 36.2, 31.5, 30.9, 29.6, 25.3, 22.6, 21.3, 21.2, 17.7, 17.2, 14.0,
 13.0, 9.6, 8.7

Step 2b. Compound of Formula I: A = -CHO, B = -CH₂NH-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

10 Into a solution of the compound of step 2a (59 mg) in THF (1 mL), was added 1N HCl (1 mL) dropwise. The reaction mixture was stirred for 40 minutes at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude residue was purified by flash
 15 chromatography (NH₄OH:MeOH:CH₂Cl₂/1:5:194) to give the title compound (46 mg).
 MS (ESI) m/z 785 (M+H)⁺.

Step 2c. Compound of Formula I: A = -CHO, B = -CH₂NH-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H. and R^P = H.

A solution of the compound of step 2b (46 mg) in methanol was stirred at room
 20 temperature for twelve hours. The solvent was evaporated under reduced pressure to give the title compound.

MS (ESI) m/z 701 (M+H)⁺.

Example 3

25 Compound of Formula I: A = -CHO, B = -CH₂-N(CH₃)-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H, and R^P = H.

Step 3a. 8 of Scheme 1: R₄ = -COCH₃, R₅ = -CH₂CH₂Phenyl, R₆ = -CH₃, R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

30 Into a solution of the crude compound from step 2a (155 mg) in acetonitrile (1.5 mL), was added formaldehyde (0.1 mL, 40% in water), acetic acid (0.1 mL) and NaCNBH₃ (56 mg, 0.9 mmol) at 0°C. The solution was stirred at 0°C for 20 minutes, then warmed to room temperature and stirred for three hours. The reaction mixture was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was

washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude compound was purified by flash chromatography ($\text{NH}_4\text{OH}:\text{MeOH}:\text{CH}_2\text{Cl}_2/1:5:94$) to give the title compound (33 mg) as a white foam.

MS (ESI) m/z 845 ($\text{M}+\text{H}$)⁺.

- 5 Step 3b. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

Into a solution of the compound of step 3a (33 mg) in THF (1 mL), was added 1N HCl (1 mL) dropwise. The reaction mixture was stirred for 40 minutes at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give pure title compound (30 mg).

MS (ESI) m/z 799 ($\text{M}+\text{H}$)⁺.

- ¹³C-NMR(100 MHz, CDCl_3): δ 203.2, 203.1, 173.8, 169.8, 169.2, 148.2, 144.8, 140.2, 134.1, 128.6, 128.3, 126.0, 117.7, 101.8, 80.8, 76.5, 71.4, 71.0, 70.5, 67.1, 66.7, 59.7, 58.9, 55.4, 45.0, 43.5, 43.3, 41.2, 40.7, 39.3, 33.6, 31.6, 31.1, 25.8, 21.3, 21.2, 17.5, 17.2, 13.0, 9.7, 8.6

Step 3c. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)-CH₂CH₂Phenyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H.

- A solution of the compound from step 3b (30 mg) in methanol (1 mL) was stirred at room temperature overnight, then concentrated under reduced pressure to give the pure title compound (27 mg).

MS (ESI) m/z 715 ($\text{M}+\text{H}$)⁺.

- ¹³C-NMR(100 MHz, CDCl_3): δ 203.1, 202.9, 173.9, 148.3, 144.9, 140.2, 134.1, 128.7, 128.6, 128.3, 126.0, 104.0, 73.3, 70.9, 70.7, 70.2, 59.7, 59.1, 44.7, 43.8, 43.3, 42.5, 41.7, 41.2, 40.6, 39.3, 35.5, 33.6, 29.7, 25.9, 23.3, 17.8, 17.4, 12.9, 9.7, 8.9.

Example 4

Compound of Formula I: A = -CHO, B = -CH₂-NH-CH₂CH₂-(2-pyridyl), R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H.

- 30 Step 4a. 8 of Scheme 1: R₄ = -COCH₃, R₅ = -CH₂CH₂-(2-pyridyl), R₆ = H, R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

The compound from step 1c (300 mg, 0.36 mmol) was treated with 2-(2-aminoethyl) pyridine (48 mg, 0.39 mmol) by following procedure described in step 2a to give the pure title compound (100mg).

MS (ESI) m/z 832 (M+H)⁺.

5 ¹³C-NMR(100 MHz, CDCl₃): δ 203.7, 173.7, 169.7, 169.2, 159.7, 149.2, 147.0, 142.4, 136.5, 136.4, 123.2, 121.4, 102.4, 102.0, 81.2, 77.2, 75.7, 71.5, 70.9, 70.5, 67.2, 53.4, 50.0, 49.9, 49.1, 45.1, 44.9, 41.2, 41.1, 39.7, 37.3, 32.8, 32.6, 30.9, 25.2, 21.3, 21.1, 17.6, 17.1, 13.1, 9.6, 8.6.

Step 4b. 8 of Scheme 1: R₄ = -COCH₃, R₅ = -CH₂CH₂-(2-pyridyl), R₆ = -CH₃, R^P₂ = -

10 COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

Into a solution of the compound from step 4a (57 mg, 0.068 mmol) in acetonitrile (1.5 mL), was added formaldehyde (0.1 mL, 40% in water), acetic acid (0.1 mL) and NaCNBH₃ (56 mg, 0.9 mmol) at 0°C. The solution was stirred at 0°C for 20 minutes, then warmed to room temperature and stirred for three hours. The reaction mixture was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude compound was purified by flash chromatography (NH₄OH: MeOH:CH₂Cl₂/1:5:94) to give the title compound (33 mg) as a white foam.

MS (ESI) m/z 846 (M+H)⁺.

20 ¹³C-NMR(100 MHz, CDCl₃): δ 203.8, 173.7, 169.7, 169.3, 160.3, 149.1, 147.8, 136.3, 133.9, 123.3, 121.2, 102.5, 102.1, 81.4, 76.5, 71.6, 71.0, 70.6, 67.3, 60.3, 58.8, 57.8, 53.5, 50.0, 45.0, 43.3, 42.3, 41.2, 39.7, 35.8, 32.7, 31.0, 29.7, 25.6, 21.3, 21.2, 17.7, 17.2, 14.2, 12.9, 9.7, 8.7.

Step 4c. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)-CH₂CH₂-(2-pyridyl), R₁

25 and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

Into a solution of the compound of step 4b (33 mg) in THF (1 mL), was added 1N HCl (1 mL) dropwise. The reaction mixture was stirred for 40 minutes at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give pure title compound (30 mg).

MS (ESI) m/z 800 (M+H)⁺.

35 ¹³C-NMR(100 MHz, CDCl₃): δ 203.2, 203.1, 173.8, 169.7, 169.2, 160.2, 149.2, 148.2, 136.3, 134.0, 123.3, 121.2, 101.8, 80.8, 76.5, 71.4, 71.0, 70.5, 67.1, 66.6, 58.9, 57.8, 45.0, 43.5, 43.2, 42.2, 41.2, 40.7, 39.3, 35.7, 31.6, 31.1, 25.7, 21.3, 21.2, 17.5, 17.2, 12.9, 9.7, 8.5.

Step 4d. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)-CH₂CH₂-(2-pyridyl), R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H.

A solution of the compound from step 4c (30 mg) in methanol (1 mL) was stirred at room temperature overnight, then concentrated under reduced pressure to give the pure title compound (28 mg).

MS (ESI) m/z 716 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.7, 203.1, 173.9, 160.2, 149.2, 148.3, 136.3, 134.0, 123.3, 121.2, 104.0, 73.3, 71.0, 70.8, 70.2, 59.1, 57.9, 53.4, 44.7, 43.8, 43.3, 42.3, 41.7, 39.3, 35.8, 29.7, 25.9, 17.8, 17.4, 12.9, 9.7, 9.0.

Example 5

Compound of Formula I: A = -CHO, B = -CH₂-4-morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H and R^P = H

Step 5a. 8 of Scheme 1: R₄ = -COCH₃, R₅ and R₆ taken together = -CH₂CH₂-O-CH₂CH₂-,

R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

Into the solution of the crude compound from step 1c (200 mg, 0.238 mmol) in acetonitrile (2 mL), was added morpholine (104 mg, 1.2 mmol) at room temperature. The reaction mixture was heated to 60°C for 4.5 hours, cooled to room temperature, stirred overnight. The reaction mixture was taken up in EtOAc, washed with brine, dried

(Na₂SO₄), filtered and concentrated under reduced pressure.

The crude compound was purified by flash chromatography (MeOH:CH₂Cl₂/2:98) to give the title compound (157 mg) as a white foam.

MS (ESI) m/z 797 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.8, 173.6, 169.6, 169.1, 147.5, 144.3, 133.7, 118.2, 102.3, 102.0, 81.2, 76.3, 71.4, 70.9, 70.5, 67.1, 66.6, 59.9, 53.8, 53.4, 53.3, 49.8, 44.9, 42.3, 41.1, 39.6, 32.8, 32.6, 30.9, 25.5, 21.2, 21.1, 17.6, 17.1, 12.8, 9.6, 8.6.

Step 5b Compound of Formula I: A = -CHO, B = -CH₂-4-morpholyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -COCH₃ and R^P = -COCH₃;

Into a solution of the compound of step 5a (157 mg) in THF (1 mL), was added 1N HCl (1 mL) dropwise. The reaction mixture was stirred for 40 minutes at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give pure title compound (150 mg).

MS (ESI) m/z 751 (M+H)⁺.

^{13}C -NMR(100 MHz, CDCl_3): δ 203.2, 202.9, 173.6, 169.6, 169.1, 147.9, 144.4, 133.8, 117.8, 101.6, 80.6, 76.3, 71.3, 70.9, 70.3, 66.9, 66.6, 66.5, 60.2, 60.0, 53.8, 44.9, 43.4, 42.2, 41.1, 40.6, 39.2, 31.5, 30.9, 25.6, 21.1, 21.0, 20.8, 17.4, 17.1, 14.0, 12.8, 9.6, 8.4.

Step 5c. Compound of Formula I: A = -CHO, B = -CH₂-4-morpholyl, R₁ and R₂ taken

5 together are = O, R₃ = H, R₄ = H, and R^P = H.

A solution of the compound from step 5b (150 mg) in methanol (4 mL) was stirred at room temperature overnight, then concentrated under reduced pressure to give the pure title compound (125 mg).

MS (ESI) m/z 667 (M+H)⁺.

10 ^{13}C -NMR(100 MHz, CDCl_3): δ 203.3, 203.0, 173.8, 148.1, 144.6, 133.8, 103.9, 76.4, 73.2, 70.8, 70.7, 70.0, 66.7, 60.1, 53.8, 50.5, 44.7, 43.6, 42.3, 41.6, 39.3, 25.7, 17.7, 17.4, 12.8, 9.6, 8.9.

Example 6

15 Compound of Formula I: A = -CHO, B = -CH₂-1-imidazolyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H, and R^P = H.

Step 6a. 8 of Scheme 1: R₄ = -COCH₃, R₅ and R₆ taken together = -CHNCH=CH-, R^P₂ = -COCH₃, R^P₃ = H, and R' = R'' = -CH₃;

20 Into the solution of the crude compound from step 1c (150 mg, 0.179 mmol) in acetonitrile (1 mL), was added imidazole (85 mg, 1.25 mmol) at room temperature. The reaction mixture was heated to 60°C for 4 hours, cooled to room temperature, stirred overnight. The reaction mixture was taken up in CHCl_3 , washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude compound was purified by flash chromatography ($\text{MeOH}:\text{CH}_2\text{Cl}_2$, 2:98) to give the title compound (37

25 mg) as a white foam.

MS (ESI) m/z 778 (M+H)⁺.

Step 6b. 8 of Scheme 1: R₄ = H, R₅ and R₆ taken together = -CHNCH=CH-, R^P₂ = H, R^P₃ = H, and R' = R'' = -CH₃;

30 A solution of the compound from step 6a (37 mg) in methanol is stirred at room temperature for twelve hours and the solvent evaporated under reduced pressure to give the title compound (35 mg).

MS (ESI) m/z 694 (M+H)⁺.

Step 6c. Compound of Formula I: A = -CHO, B = -CH₂-1-imidazolyl, R₁ and R₂ taken together are = O, R₃ = H, R₄ = H, and R^P = H.

Into a solution of the compound of step 6b (35 mg) in THF (1 mL), was added 1N HCl (1 mL) dropwise. The reaction mixture was stirred for 40 minutes at room temperature, then was basified with a solution of saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give pure title compound (32 mg).

MS (ESI) m/z 648 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.0, 202.8, 173.6, 146.8, 139.4, 137.1, 136.9, 129.8, 118.8, 103.9, 74.6, 73.3, 70.9, 70.7, 70.1, 60.3, 47.8, 46.8, 44.5, 43.7, 41.7, 39.4, 25.5, 17.8, 17.2, 12.7, 9.6, 8.9.

Example 7

Compound of Formula I: A = -CHO, B = -CH₂-N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -CH₂CHCH-(3-quinolyl), and R^P = H.

Step 7a. 8 of Scheme 1: R₄ = -COCH₃, R₅ = R₆ = -CH₃, R^P₂ = -COCH₃, R^P₃ = TMS, and R' = R'' = -CH₃;

To the crude compound from step 1d (5.2 g, 6.82 mmol) in 1-methylimidazole (20 mL), was added 1,1,1,3,3,3-hexamethyl disilazane (1.72 mL, 8.16 mmol). After stirring at room temperature for 5.5 hrs, the reaction mixture was diluted with ethyl acetate, washed with water, then with brine, and dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a yellow syrup. The compound was purified by flash chromatography (ethyl acetate) to give 4.6 g of the title compound (82% from the compound of step 1b). MS (ESI) m/z 827 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.7, 171.5, 169.5, 169.0, 147.5, 144.4, 133.6, 118.3, 101.7, 100.4, 78.4, 76.0, 71.4, 70.7, 70.3, 68.1, 67.1, 60.8, 53.6, 49.0, 45.6, 43.3, 41.6, 41.1, 36.2, 32.7, 32.1, 29.5, 25.5, 21.2, 21.0, 17.7, 17.2, 13.9, 12.7, 9.5, 8.7, 0.2.

Step 7b. 8 of Scheme 1: R₄ = H, R₅ = R₆ = -CH₃, R^P₂ = H, R^P₃ = TMS, and R' = R'' = -CH₃;

A mixture of the compound from step 7a (4.5 g, 5.4 mmol) and methanol (40 mL) was stirred at room temperature overnight and concentrated under reduced pressure to give 4.0 g of the title compound.

MS (ESI) m/z 743 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.8, 171.6, 147.9, 144.7, 133.7, 118.5, 102.7, 101.8, 78.4, 76.1, 73.1, 71.3, 70.6, 70.1, 68.4, 61.0, 53.7, 45.8, 43.4, 41.7, 36.7, 33.4, 32.3, 25.6, 21.3, 21.2, 17.9 (2C), 12.8, 9.6, 9.4, 0.3.

Step 7c. Compound of Formula I: A = -CH(OCH₃)₂, B = -CH₂N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = TMS, R₄ = -CH₂CHCH-(3-quinolyl), and R^P = H;

Into a degassed solution of the compound from step 7b (410 mg, 0.55 mmol) and 1-(3-quinolyl)-2-propen-1-ol-*t*-butyl carbonate (171 mg, 0.60 mmol) in THF (4 mL) were
 5 added Pd₂(dba)₃ (46 mg, 0.05 mmol), and dppb (42 mg, 0.1 mmol). The mixture was stirred at room temperature for 15 mins, heated to 65°C for 2 hrs, then cooled to room temperature. The mixture was filtered through a short plug of silica gel (eluting with ethylacetate). The eluant was concentrated under reduced pressure to provide the resulting crude mixture of the title compound (120 mg).
 10 MS (ESI) m/z 910 (M+H)⁺.

Step 7d. Compound of Formula I: A = -CHO, B = -CH₂N(CH₃)₂, R₁ and R₂ taken together are = O, R₃ = H, R₄ = -CH₂CHCH-(3-quinolyl), and R^P = H.

Into a solution of the crude compound from step 7c (120 mg) in THF (1 mL) at 0°C was added 1N HCl (1 mL). The mixture was stirred at 0°C for 2 hrs and quenched by
 15 addition of a saturated solution of NaHCO₃. The resulting aqueous solution was extracted with CHCl₃. The extract was concentrated under reduced pressure. The crude residue was purified on reversed phase HPLC to give the title compound.
 MS (ESI) m/z 792 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 203.5, 174.2, 149.4, 148.4, 147.6, 144.8, 134.7, 132.9,
 20 129.5 (2C), 129.4, 128.9, 128.4, 128.0, 127.2, 117.9, 103.8, 102.4, 81.7, 80.0, 76.5, 73.3, 71.9, 70.4, 70.1, 67.2, 61.3, 46.0, 45.3, 44.0, 43.6, 41.9, 41.1, 39.7, 32.7, 31.5, 26.0, 18.3, 17.7, 13.1, 9.9, 9.0.

Although the invention has been described with respect to various preferred
 25 embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.